

REMARKS

Claims 1-120 are pending. With this amendment, claims 7, 15, 17-19, 24-48, 53-65, 69-73, and 101-120 have been cancelled without prejudice. Applicants reserve the right to prosecute the subject matter of cancelled claims 7, 15, 17-19, 24-48, 53-65, 69-73, and 101-120 in one or more divisional or continuation applications. With this amendment, new claims 121-127 have been added. Thus, upon entry of the present amendment, claims 1-6, 8-14, 16, 20-23, 49-52, 66-68, 74-100, and 121-127 will be pending.

With this amendment, claims 1-2, 4-6, 8-9, 11-14, 16, 20-23, 49-52, 66-68, 74, 81-83, 85, 87, 89-92, 94-95, and 97-100 have been amended for clarity and or to further recite aspects of Applicant's invention with greater particularity. Support for the amendments to claims 1-2, 4-6, and 13, and for new claims 121-127 is given in the table below.

Claim	Support in Specification
<p>1. (Currently amended) A method for constructing a variant set for an antibody of interest, the method comprising:</p> <p style="margin-left: 20px;">(a) a identifying, using a plurality of rules, a plurality of positions in said antibody of interest and, for each respective position in said plurality of positions, one or more substitutions for the respective position, wherein the plurality of positions and the one or more substitutions for each respective position in the plurality of positions collectively define an antibody sequence space;</p> <p style="margin-left: 20px;">(b) b selecting a <u>first plurality of variants</u> of the <u>antibody of interest</u>, thereby forming a variant set, wherein said variant set comprises a plurality of variants of said antibody of interest and wherein said variant set is a subset of said antibody sequence space;</p> <p style="margin-left: 20px;">(c) e measuring a property of all or a portion of the variants in said variant set;</p> <p style="margin-left: 20px;">(d) d modeling a sequence-activity relationship</p>	<p>Page 11, lines 12-22</p> <p>Page 12, lines 12-26</p> <p>Page 12, line 28, through page 13, line 2</p> <p>Page 13, lines 4-6; page 50, line 19,</p>

Claim	Support in Specification
<p>between (i) one or more substitutions at one or more positions of the antibody of interest represented by <ins>in</ins> the variant set and (ii) the property measured for all or said portion of the variants in the variant set, <u>and then deriving from the sequence-activity relationship:</u></p> <p style="padding-left: 2em;">(A) <u>a plurality of first values, wherein each first value in the plurality of first values is the contribution to the measured property by the one or more substitutions at one or more positions in the plurality of positions in the antibody of interest, and</u></p> <p style="padding-left: 2em;">(B) <u>a plurality of second values, wherein each second value in the plurality of second values quantifies a confidence of a first value in the plurality of first values; and</u></p> <p style="padding-left: 2em;">(e) e redefining said variant set to comprise variants <ins>in said antibody sequence space</ins> that include substitutions in said plurality of positions that are selected based on a function of said sequence-activity relationship plurality of first values and said plurality of second values; and</p> <p style="padding-left: 2em;">(f) <u>measuring a property of all or a portion of the variants in said variant set after said variant set has been redefined in step (e).</u></p>	<p>through page 62, line 9, and, in particular page 61, line 31, through page 62, line 9</p> <p>Page 13, line 15, through page 14, line 2; Section 5.4.2, beginning on page 64, line 25</p> <p>Page 13, line 15, through page 14, line 2</p>
<p>2. (Currently amended) The method of claim 1, the method further comprising repeating said measuring <u>step (c), said modeling step (d), and, optionally, said redefining step (e), and said measuring step (f) until a variant in said variant set exhibits a value for said property that exceeds a predetermined value.</u></p>	<p>Page 13, line 15, through page 14, line 2; page 74, lines 23-26</p>

Claim	Support in Specification
4. (Currently amended) The method of claim 1, the method further comprising repeating said measuring <u>step (c)</u> , <u>said</u> modeling <u>step (d)</u> , <u>and, optionally</u> , <u>said</u> redefining <u>step (e)</u> , <u>and said measuring step (f)</u> until a variant in said variant set exhibits a value for said property that is less than a predetermined value.	Page 13, line 15, through page 14, line 2; page 74, lines 23-26
5. (Currently amended) The method of claim <u>1</u> <u>[[4]]</u> , wherein <u>said predetermined value</u> is a value that is less than the value for the property that is exhibited by <u>said antibody of interest</u> <u>plurality of positions</u> and the one or more substitutions for each respective position in the <u>plurality of positions</u> are identified in step (a) using a <u>plurality of rules</u> .	Page 11, line 12, through page 12, line 10
6. (Currently amended) The method of claim <u>5</u> , <u>1</u> , the method further comprising repeating said measuring, modeling, and optionally, <u>said redefining</u> , a predetermined number of times wherein each rule in the <u>plurality of rules</u> defines an action to be taken in response to a computational test selected from the group of computational tests consisting of: <ul style="list-style-type: none"> <li data-bbox="375 2749 1831 3032">(i) a proximity of a position in the <u>plurality of positions</u> to a structurally defined region within the <u>antibody</u>; <li data-bbox="375 3062 1798 3345">(ii) a physico-chemical property of an amino acid at a position within a <u>plurality of antibody sequences</u>; <li data-bbox="375 3379 1847 3653">(iii) a principal component analysis of amino acids found at one or more positions within a <u>plurality of antibody sequences</u>; 	Page 20, line 31, through page 21, line 18 Page 11, lines 12-14 Page 21, line 28

Claim	Support in Specification
<p><u>(iv) a presence or an absence of a substitution in an antibody that is homologous to said antibody of interest;</u></p>	<p>Page 21, line 19, through page 22, line 22</p>
<p><u>(v) a presence or an absence of a substitution in a specific class of antibodies that are homologous to said antibody of interest;</u></p>	<p>Page 21, line 19, through page 22, line 22, in particular, page 22, lines 6-9</p>
<p><u>(vi) a favorability of a substitution to a position in the antibody of interest calculated using a substitution matrix;</u></p>	<p>Page 17, lines 9-16</p>
<p><u>(vii) a probability of a substitution to a position in the antibody of interest calculated from a conservation index;</u></p>	<p>Page 20, line 19-25</p>
<p><u>(viii) a favorability of a substitution to a position in the antibody of interest calculated from a comparison of homologous sequences;</u></p>	<p>Section 5.1.4, beginning on page 31, line 10</p>
<p><u>(ix) a mutability of a position in the antibody of interest calculated from a comparison of homologous sequences;</u></p>	<p>Page 31, line 28, through page 33, line 27</p>
<p><u>(x) a favorability of a substitution to a position in the antibody of interest calculated from a comparison of structures that are homologous to said antibody of interest; and</u></p>	<p>Section 5.1.5, beginning on page 33, line 28</p>
<p><u>(xi) a mutability of a position in the antibody of interest calculated from a comparison of structures that are homologous to said antibody of interest.</u></p>	<p>Section 5.1.5, beginning on page 33, line 28</p>
<p>13. (Currently amended) The method of claim 1, wherein said redefining <u>step (e)</u> further comprises:</p> <p><u>computing, for each respective first value in the plurality of first values, a modified respective first value by modifying the respective first value based on a</u></p>	<p>Page 61, line 31, through page 62, line 9; page 69, line 20, through page 71, line 2</p>

Claim	Support in Specification
<p><u>function of a second value, in the plurality of second values, that corresponds to the respective first value, thereby computing a plurality of modified first values; and</u></p> <p>computing a predicted score, <u>for each respective variant in [[for]] a population of variants of said antibody of interest, using said sequence-activity relationship the plurality of modified first values, thereby computing a plurality of predictive scores, wherein each variant in said population of variants includes a substitution at one or more positions in said plurality of positions in said antibody of interest; and</u></p> <p><u>selecting redefining said variant set by selecting variants from among said population of variants as a function of the predicted score received by each variant in said set of variants.</u></p>	
121. (New) The method of claim 1, wherein a second value in the plurality of second values is a standard deviation of a corresponding first value in the plurality of first values.	Page 61, line 34, through page 62, line 3
122. (New) The method of claim 1, wherein each variant in the redefined variant set of step (e) differs by fewer than 5 substitutions from at least one variant for which the property has been measured in step (c).	Section 5.4.3, beginning on page 67, line 15; for example, page 68, lines 6-9 and 24-27
<p>123. (New) The method of claim 1 wherein said redefining of said variant set further comprises:</p> <p>computing a modified first score in the plurality of first scores by modifying the first score based on a</p>	Page 56, lines 25-28

Claim	Support in Specification
<p>function of the second score, in the plurality of second scores, that corresponds to the first score, thereby computing a plurality of modified first scores; and</p> <p>wherein said function of said plurality of first values and said plurality of second values comprises using the modified first score for each of the one or more substitutions at the plurality of positions as a basis for including or excluding substitutions from the redefined variant set.</p>	
<p>124. (New) The method of claim 5, wherein</p> <p>the contribution of each respective rule in the plurality of rules to the defining of said antibody sequence space is independently weighted by a rule weight in a plurality of rule weights corresponding to the respective rule; and</p> <p>the plurality of rule weights are calculated based on a comparison, for a plurality of substitutions in the variant set of (i) a value assigned to the respective substitution by the sequence-activity relationship, and (ii) a score assigned by the plurality of rules to the respective substitution.</p>	Section 5.1.3, beginning on page 28
<p>125. (New) The method of claim 1, wherein said modeling a sequence activity relationship step (d) comprises deriving a relationship between (i) a physico-chemical property of one or more substitutions at one or more positions of the antibody of interest represented by the variant set and (ii) the property measured for all or the portion of the variants in the variant set.</p>	Section 5.3, beginning on page 50, line 16

Claim	Support in Specification
<p>126. (New) The method of claim 1, wherein said redefining said variant set step (e) comprises: selecting one or more substitutions in the plurality of positions based on a comparison of:</p> <p>(i) a physico-chemical property of a substitution incorporated into the redefined variant set of step (e),</p> <p>(ii) a physico-chemical property of a substitution whose contribution to the measured property of the antibody of interest at the corresponding position has been calculated from the sequence-activity relationship, or</p> <p>(iii) a value quantifying the confidence with which said contribution to the measured property by the one or more substitutions at one or more positions of the antibody of interest can be assigned.</p>	Page 54, lines 11-13
<p>126. (New) The method of any one of claims 1-6, 8-14, 16, 20-23, 49-52, 66-68, 74-100, or 121-125 implemented on a computer.</p>	Figure 1; page 14, line 5, through page 15, line 30
<p>127. (New) A computer program product encoding instructions for implementing the method according to any one of claims 1-6, 8-14, 16, 20-23, 49-52, 66-68, 74-100, or 121-125.</p>	Page 122, lines 1-9

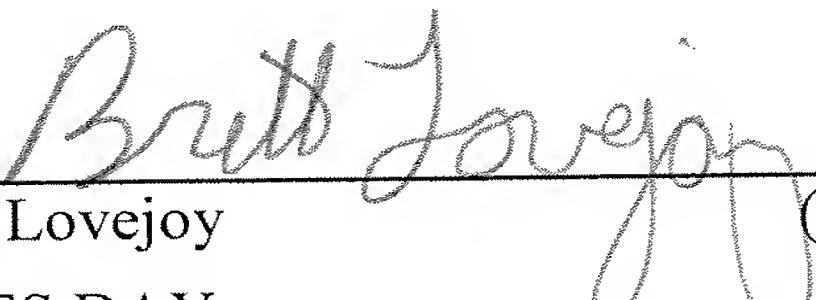
Furthermore, with this amendment, typographical errors in the specification have been corrected. No new matter has been added by way of the claim amendments, the new claims, or the amendments to the specification.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks into the file of the above-identified application. If any fees are due in connection with this submission, please charge the required fee to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

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